

Sustained haemodynamic action of nitroglycerin ointment¹

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Intravenous vasodilators have been shown to improve the haemodynamic status of patients in congestive heart failure. However, neither intravenous nor sublingual preparations are suitable for chronic administration or use in ambulatory patients. In this study, nitroglycerin ointment was administered to 11 patients in congestive heart failure. Mean pulmonary wedge and arterial pressures, as well as systemic blood pressures and heart rate were then monitored for 2 to 5 hours and compared with baseline values. Pulmonary wedge and arterial pressures, as well as systemic systolic arterial pressure, decreased significantly at 15 minutes after application and remained depressed for up to 5 hours. Systemic diastolic pressures fell significantly at 30 minutes and also remained significantly reduced for up to 5 hours. Thus, nitroglycerin ointment may be suitable for chronic vasodilator therapy of congestive heart failure.

Acute administration of systemic vasodilating drugs has been shown to improve the haemodynamic status of patients in congestive heart failure, with and without acute myocardial infarction (Miller *et al.*, 1975; Flaherty *et al.*, 1975; Shell and Sobel, 1974; Walinsky *et al.*, 1974). The nitrates and phentolamine have in fact been effective in some patients refractory to conventional therapy (Guiha *et al.*, 1974; Gold, Leinbach, and Sanders, 1972; Majid, Sharma, and Taylor, 1971).

Most studies to date have used potent, rapid acting intravenous preparations of sodium nitroprusside, nitroglycerin, phentolamine, or trimethaphan. These require intensive haemodynamic monitoring and precise control of infusion rates to avoid induction of dangerous systemic hypotension (Guiha *et al.*, 1974; Walinsky *et al.*, 1974). This manner of administration is necessarily restricted to the intensive care setting. More general clinical applicability would require a long-acting vasodilator preparation suitable for administration without intravenous infusion or frequent haemodynamic monitoring. Oral nitrate preparations have been proposed for this purpose (Franciosa *et al.*, 1974;

Kasparian *et al.*, 1975), but controversy persists regarding their efficacy and resistance to rapid hepatic transformation (Goldstein *et al.*, 1971; Needleman, Lang, and Johnson, 1972).

Cutaneously administered nitroglycerin has the theoretical advantage of enhanced bioavailability because of direct absorption into the systemic circulation. It is similar in this regard to sublingual and intravenous preparations whose activity is readily seen but of brief duration (Goldstein *et al.*, 1971; Goldstein and Epstein, 1973; Klaus *et al.*, 1973). The cutaneous route might provide sustained activity on the basis of continuous absorption from a sizeable depot on the skin. In this connexion, nitroglycerin ointment has recently been shown to improve exercise tolerance in angina pectoris patients for at least 3 hours (Reichek *et al.*, 1974).

The present study was undertaken to determine whether nitroglycerin ointment causes nitrate-like haemodynamic effects of sufficient magnitude and duration to be of potential value in therapy of congestive heart failure.

Methods

Eleven consecutive patients clinically suspected of having significant left ventricular dysfunction, and found to have pulmonary wedge pressures greater

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TABLE 1 Biographical data and baseline haemodynamic values

Case No.	Age (y)	Sex	Diagnosis	PWP (mmHg)	PAP (mmHg)	SSP (mmHg)	SDP (mmHg)	Heart rate (beats/min)	Dose of nitroglycerin ointment
1	63	M	AMI	28	39	111	80	92	5 cm, 2%
2	62	F	AMI	20	25	153	100	96	2.5 cm, 2%
3	75	M	CAD	40	51	135	100	120	5 cm, 2%
4	40	M	MHT	24	25	173	125	80	2.5 cm, 2%
5	49	F	AMI	14	19	174	101	94	2.5 cm, 2%
6	49	M	CAD	21	29	116	81	70	2.5 cm, 2%
7	58	M	AMI	23	30	142	97	86	2.5 cm, 2%
8A*	45	M	CAD	31	38	89	70	100	5.0 cm, 4%
8B*	45	M	CAD	36	40	79	60	92	5.0 cm, 2%
9	32	M	MHT	19	33	212	131	66	5.0 cm, 2%
10	74	F	AR	29	45	161	83	87	5.0 cm, 2%
11	50	M	AMI	29	40	122	90	112	2.5 cm, 2%
Mean \pm SEM				26 \pm 2.2	34.5 \pm 2.7	138.9 \pm 11.1	93.2 \pm 6.0	91.3 \pm 4.5	

Abbreviations: AMI, acute myocardial infarction; CAD, chronic coronary arterial disease; MHT, malignant hypertension; AR, aortic valvular regurgitation; PWP, pulmonary wedge mean pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure.

*Same patient studied on two separate occasions.

than 14 mmHg were included in the study. Patients' age, sex, cardiac diagnosis, and control haemodynamic values are listed in Table 1. One patient was studied on two separate occasions at an interval of 10 days before and after ventricular aneurysmectomy. No patient was given digitalis for the first time on the day of study. No patient previously on digitalis received greater than a maintenance dose of a digitalis preparation on the day of study. Only intravenous frusemide was used for diuresis and this was not administered within 4 hours before entry into the study. Informed written consent was obtained from all patients before study. Right heart catheterization was performed at the bedside, using No. 7 French Swan-Ganz catheters (Swan *et al.*, 1970). Right heart pressures were measured, using an Ailtech Model M510 transducer and a Tektronix Model 412 pressure amplifier. Zero reference point was taken at the mid chest. Systemic systolic and diastolic pressures were measured by sphygmomanometry. Control values for pulmonary wedge pressure, pulmonary arterial pressure, systemic systolic and diastolic pressure, and heart rate were obtained twice at an interval of 30 minutes. No patient whose second control value for pulmonary wedge pressure was more than 5 mmHg below the first value or less than 14 mmHg was included in the study. Control values were taken as the average of both readings. Immediately after the second control reading, 2.5 cm 2 per cent nitroglycerin ointment was applied to a 232 cm² area of skin on the back or thighs and covered with an oc-

clusive plastic dressing. Haemodynamic measurements were then made at 15-minute intervals. If no appreciable fall in pulmonary wedge pressure was seen within 30 minutes, a second 2.5 cm nitroglycerin ointment was applied to another 232 cm² area and measurements were repeated. If there was still no fall in pulmonary wedge pressure (Case 8A) the 2 per cent nitroglycerin ointment was removed and replaced by 5 cm 4 per cent nitroglycerin ointment applied to two separate 232 cm² areas. Once a fall of pulmonary wedge pressure >5 mmHg was observed, subsequent measurements were made at 30 to 60 minute intervals for 2 to 5 hours.

Control pressures and heart rates were expressed as mean \pm standard error of the mean (SEM). The haemodynamic changes attributed to nitroglycerin ointment were expressed as mean differences from control values \pm standard error of the difference (SED). Statistical evaluation was performed using Student's *t* test for paired data.

In view of the necessity to withhold inotropic or diuretic agents during the study period, use of a placebo ointment was considered unjustified.

Results

Nitroglycerin ointment caused significant reductions in pulmonary wedge pressure, pulmonary arterial pressure, and systemic blood pressures that were maintained for up to 5 hours. Mean differences

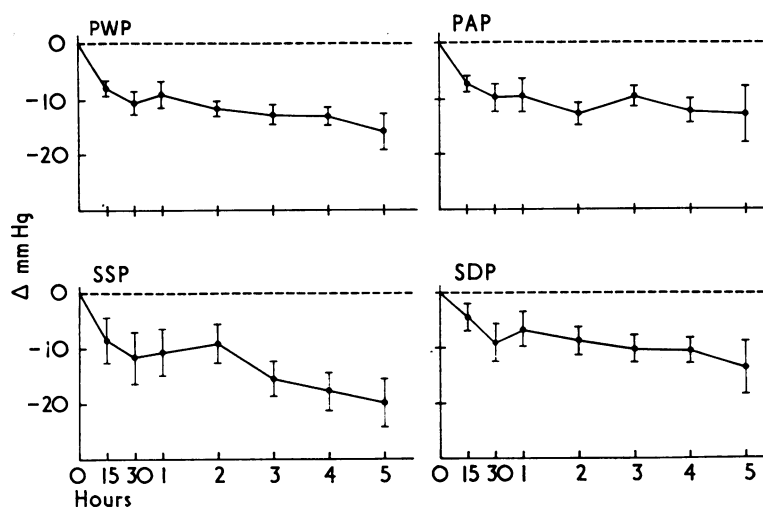


FIG. 1 Haemodynamic changes after application of nitroglycerin ointment. Results as mean differences from baseline \pm SED. PWP, pulmonary wedge mean pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure.

from control for all values are listed in Table 2 and illustrated in Fig. 1.

Pulmonary wedge pressure was significantly reduced by 7.9 mmHg at 15 minutes ($P < 0.005$). Maximum reductions of 12.9 mmHg and 15.8 mmHg occurred at 4 and 5 hours, respectively ($P < 0.005$ for both).

Similarly, pulmonary artery pressure was significantly reduced by 7.3 mmHg ($P < 0.005$) at 15 minutes. Peak reductions were 12.1 mmHg and 12.9 mmHg at 4 and 5 hours ($P < 0.005$ and < 0.05).

Systemic systolic pressure was also significantly reduced at 15 minutes by 8.5 mmHg ($P < 0.05$).

Again, peak effect was observed at 4 and 5 hours when reductions were 17.7 mmHg and 19.8 mmHg, respectively ($P < 0.005$ and < 0.025).

The reduction in systemic diastolic pressure was not significant until 30 minutes and was 9.0 mmHg ($P < 0.025$) at that time. Again, peak reductions of 10.5 mmHg and 13.5 mmHg were noted at 4 and 5 hours ($P < 0.005$ and < 0.05 , respectively).

Five of six patients showed return of haemodynamic levels toward normal within one hour of removal of nitroglycerin ointment.

Although no attempt was made to quantify symptoms or physical signs, 4 patients who were dyspnoeic during the control period had relief of

TABLE 2 Changes in haemodynamic parameters after administration of nitroglycerin ointment

	15 min	30 min	1 hr	2 hr	3 hr	4 hr	5 hr
PWP (mmHg)	*** -7.9 \pm 1.5	*** -10.6 \pm 2.3	*** -9.0 \pm 2.4	*** -12.5 \pm 2.4	*** -12.7 \pm 1.8	*** -12.9 \pm 1.7	** -15.8 \pm 3.3
PAP (mmHg)	*** -7.3 \pm 1.5	*** -9.6 \pm 2.5	*** -9.4 \pm 2.9	*** -12.8 \pm 2.1	*** -9.5 \pm 1.7	*** -12.1 \pm 2.1	* -12.9 \pm 5.1
SSP (mmHg)	* -8.5 \pm 4.2	** -11.6 \pm 4.6	** -10.8 \pm 4.2	** -9.0 \pm 3.6	*** -15.3 \pm 3.2	*** -17.7 \pm 3.4	** -19.8 \pm 4.3
SDP (mmHg)	-4.4 \pm 2.4	-9.0 \pm 3.4	-6.6 \pm 3.2	-8.7 \pm 2.5	-10.3 \pm 2.4	-10.5 \pm 2.4	-13.5 \pm 4.7
HR (beats/min)	-0.8 \pm 1.9	-1.1 \pm 3.5	-2.9 \pm 3.0	-1.2 \pm 3.8	-0.3 \pm 4.5	-3.9 \pm 3.6	-8.5 \pm 5.3
No. of patients	10	10	12	12	11	11	4

Abbreviations: PWP, pulmonary wedge pressure; PAP, pulmonary arterial mean pressure; SSP, systemic arterial systolic pressure; SDP, systemic arterial diastolic pressure; HR, heart rate; * = $P < 0.05$; ** = $P < 0.025$; *** = $P < 0.005$.

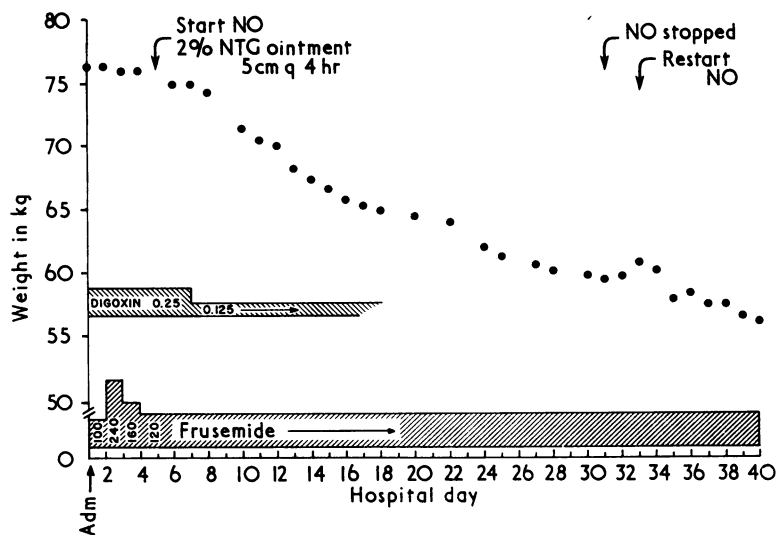


FIG. 2 Daily weights in Case 10 with severe biventricular failure who was treated with maintenance nitroglycerin ointment (NO) in addition to digoxin and frusemide (see text).

this symptom after nitroglycerin ointment was applied. A 74-year-old woman (Case 10) had severe biventricular failure and anasarca on the basis of aortic regurgitation. After 4 days of treatment with bed rest, sodium restriction, digoxin, and high doses of frusemide, she had lost only 0.45 kg. She was then admitted to this study and given 5 cm 2 per cent nitroglycerin ointment which reduced her pulmonary wedge pressure from 29 to 12 mmHg, and her dyspnoea improved. Subsequently, she was maintained on this dose of nitroglycerin ointment every 4 hours, as well as maintenance digoxin and frusemide, and had prompt onset of a sustained diuresis. Her daily weights and medicines given are plotted in Fig. 2. When nitroglycerin ointment was discontinued for 3 days she regained 1.8 kg. Weight loss then resumed when nitroglycerin ointment was reinstituted.

No patient developed symptoms or physical signs of systemic arterial hypotension during the study. Several patients complained of headache. One patient noted mild burning at the site of 4 per cent nitroglycerin ointment application.

Discussion

The beneficial effects of sublingual or intravenous vasodilating drugs in congestive heart failure have been attributed to simultaneous reduction of left ventricular outflow impedance and filling pressure caused, respectively, by arteriolar and venous vaso-

dilatation. These changes permit the left ventricle to operate at a smaller cavity size with consequently improved mechanical efficiency and reduced myocardial oxygen demand. The observed haemodynamic effects include distinct reduction in pulmonary wedge pressures and modest reduction in systemic arterial pressures without change in heart rate (Miller *et al.*, 1975; Gold *et al.*, 1972; Flaherty *et al.*, 1975; Franciosa *et al.*, 1972). Cardiac output response is variable and appears to be a function of left ventricular filling pressure (Miller *et al.*, 1975; Gold *et al.*, 1972; Johnson, Fairley, and Carter, 1959; Walinsky *et al.*, 1974; Williams, Amsterdam, and Mason, 1975). Since our intention was to examine the duration of action of nitroglycerin ointment, only those variables known to change unidirectionally in response to vasodilators were monitored, and cardiac output was not included.

In this study, administration of nitroglycerin ointment to patients with left ventricular dysfunction resulted in significant lowering of pulmonary wedge pressure, pulmonary arterial pressure, and systemic arterial pressures, characteristic of that seen with intravenous or sublingual vasodilators. Significant reductions were usually noted at 15 to 30 minutes after application and a significant effect persisted for up to 5 hours. Clinically important hypotension was not encountered. Though considerable individual variation was noted, average coronary perfusion pressure (estimated by subtraction of wedge pressure from systemic diastolic

pressure) was not significantly decreased at any measured interval.

Not surprisingly, the size of the application area played a critical role in producing these haemodynamic effects. No appreciable haemodynamic changes were observed when smaller, 103 cm², application areas were used. Furthermore, about half of our subjects required a doubling of the initial dose and application area for achievement of an adequate response.

For the purpose of this study, reduction of pulmonary wedge pressure was used as an objective indicator of drug effectiveness. Our experience suggests that for routine use it would be sufficient to monitor systemic blood pressure while increasing the dose and application area until a satisfactory clinical response is observed. In this connexion, 3 of our study patients who were symptomatic and poorly responsive to conventional therapy for congestive heart failure were maintained on nitroglycerin ointment after the study. All reported improvement in their congestive symptoms, and untoward effects other than headaches were not observed. The clinical course in one patient with biventricular failure and anasarca has been described above and in Fig. 2.

The sustained haemodynamic activity observed in our study suggests that nitroglycerin ointment may prove applicable to other disease states for which vasodilator therapy is appropriate, such as in prophylaxis of angina pectoris. Though this study did not deal specifically with angina, our demonstration of sustained pharmacological activity is consistent with the exercise studies of Reichek *et al.* (1974).

Recent studies in both experimental animals and man suggest that vasodilator therapy during acute myocardial infarction may limit the extent and sequelae of myocardial necrosis (Flaherty *et al.*, 1975; Shell and Sobel, 1974; Smith *et al.*, 1973; Borer *et al.*, 1974). If future investigations confirm these findings, nitroglycerin ointment may provide a convenient means of reducing myocardial oxygen demand in routine management of acute myocardial infarction.

In summary, our data indicate that nitroglycerin ointment causes a sustained haemodynamic response similar to that seen with acutely administered vasodilators. With careful adjustment of dosage and application area it can be used in ambulatory patients without induction of dangerous hypotension. Accordingly, it has potential value in chronic vasodilator therapy of congestive heart failure and merits consideration for use in other clinical situations for which sustained vasodilatation is appropriate.

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